

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: MICHAEL A. GOLLIN VENABLE LLP P. O. BOX 34385 WASHINGTON, DC 20043-9998

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 58086-241960		Date of mailing (day/month/year) 16 JUN 2008
FOR FURTHER ACTION See paragraph 2 below		
International application No. PCT/US06/34374	International filing date (day/month/year) 05 September 2006 (05.09.2006)	Priority date (day/month/year) 02 September 2005 (02.09.2005)
International Patent Classification (IPC) or both national classification and IPC IPC: A61K 38/26 (2006.01), 31/56 (2006.01) USPC: 514/178,12		
Applicant THE REGENTS OF THE UNIVERSITY OF CALIFORNIA		

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the opinion |
| <input type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> | Box No. VIII | Certain observations on the international application |


2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Date of completion of this opinion 06 June 2008 (06.06.2008)	Authorized officer YONG S. CHONG  Telephone No. (571)-272-0700
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US06/34374

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
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International application No.
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Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>NONE</u>	YES
	Claims <u>1-48</u>	NO
Inventive step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-48</u>	NO
Industrial applicability (IA)	Claims <u>1-48</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1-48 lack novelty under PCT Article 33(2) as being anticipated by Parhami (US Patent Application 2006/0270645 A1).

Parhami teach agents and methods for inducing osteoblastic cellular differentiation as well as methods to treat patients with bone disorders. Exemplary agents include oxysterols (abstract). Osteoblasts come from a pool of marrow stromal cells (also known as mesenchymal stem cells, MSC). These cells are present in a variety of tissues. MSC is pluripotent and can differentiate into adipocytes (paragraph 0003). The present invention also encompasses methods of treating osteoporosis (paragraphs 0004-0012). Agents which are useful in this invention include 22(R)-, 22(S)-, 20(S)-, and 25-hydroxycholesterol, bisphosphonates, sodium fluoride, insulin-like growth factors I and II and transforming growth factor beta (paragraphs 0014-0015). Oxysterols induce osteogenic differentiation and mineralization and inhibit adipogenic differentiation (paragraph 0035). The in vitro models used to show the osteogenic and anti-adipogenic effects of oxysterols are valid and have been used to previously in demonstrating similar behaviors of other compounds including bone morphogenetic proteins (BMP) (paragraph 0038). The effect of oxysterols have been demonstrated to be potentiated by a cytochrome P450 inhibitor, phospholipase A2, arachadonic acid, and ERK, therefore can be used in combination with oxysterols (paragraph 0040, 0050). The invention may include a method of systemic delivery or localized treatment with differentiated osteoblastic cells. In this embodiment, mammalian mesenchymal stem cells may be harvested, treated with at least one agent to induce osteoblastic differentiation of the cells, and then readministered to the patient at the site at which bone repair is desired (paragraph 0052). An implant may be used, for example pins, screws, plates, or prosthetic joints (paragraph 0058).

It is noted that the limitations regarding the etiology of a disease, for example, oxidative stress, will be given little patentable weight because it is considered preamble. Furthermore, the origin or cause of a disorder has no bearing on the symptoms and treatment regimen. It is also noted that the mechanism of action and properties of an active agent are inherent if that particular active agent is disclosed.

Claims 1-48 meet the criteria set out in PCT Article 33(4), and thus has industrial applicability because the subject matter claimed can be made or used in industry.